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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Maes, et al.

Serial No.: 09/773,351 Group Art Unit: 1617

Filed: January 31, 2001 Examiner: Jiang, Shaojia A.

For: Cholesterol Sulfate and Amino Sugar Compositions for Enhancement of Stratum Corneum Function

RESPONSE PURSUANT TO 37 CFR 1.113 AND 1.116

REMARKS

Assistant Commissioner of Patents and Trademarks

Washington, D.C. 20231

Dear Sir:

In response to the Examiner's Final Action dated May 6, 2003, please consider the accompanying remarks which are believed to place the application in condition for allowance or in better condition for appeal in the event the final rejection is maintained. Two months extension of time is requested under 37 CFR 1.136.

U.S. Patent No. 5,650,166 ("the '166 Ribier reference")

In the present action, the Examiner finds that the '166 Ribier reference renders the present claims obvious because it teaches a composition comprising cholesterol sulfate, see column 3, lines 66 – 67, and N-acetylglucosamine (NADG), see column 5, line 67. Applicant's previous argument is summarized by the Examiner as being that there is no separation or vehicle taught in the '166 Ribier reference for the combination of NADG and cholesterol sulfate, and therefore, the '166 Ribier reference fails to teach or suggest a feature of the present invention. In response to this, the Examiner notes that it is irrelevant whether the '166 Ribier reference teaches or suggest this feature because it is well within the skill of the artisan to incorporate this routine skill in the art. Applicants note that the summary of their argument is not complete. The missing feature pointed out between the '166 Ribier reference and the present invention is the presence of the combination of the NADG and cholesterol sulfate in the '166 Ribier reference in discrete layers of a lipid vesicle. Because these two ingredients are used to form discrete layers of a lipid vesicle they are not "mixed" as they are in the present invention.

The claims of the present invention have been previously amended such that the mixture of cholesterol sulfate and exfoliant, N-acetyl glucosamine is added to a pharmaceutical or cosmetically acceptable vehicle. The addition of the two ingredients at issue with respect to the '166 Ribier reference is worthy of note because this where the difference between the '166 Ribier reference and the present invention lies. The '166 reference only discloses the use of these two ingredients to form lipid vesicles, where the discrete layers are formed and the ingredients are separate by virtue of their being present in separate and discrete layers of the lipid vesicle. The cholesterol sulphate is taught at column 3, lines 57 to 67, of the '166 Ribier reference as being an additive to the lipid membrane of the vesicle. Further, one of the actives contained within the lipid vesicle with deep down action are taught at column 5, lines 59 to 67, to include inter alia, NADG. Thus, there is no mixing of these ingredients as they are in the present invention by adding them in combination to a vehicle. Unlike the present invention, the '166 Ribier vesicles contain these two ingredients in separate and distinct layers and the vehicle containing them in separate layers is added to a medium as taught at column 8, lines 32 to 35. This is in contrast to adding the ingredients themselves directly to a vehicle. This is especially the case for N-acetylglucosamine (NADG) as the '166 reference fails to teach or suggest adding the NADG directly to a vehicle because it teaches that the NADG is contained within the lipid vesicle. Therefore, even though the vesicle is added to a vehicle, because the NADG is inside the vesicle, there is no teaching in the '166 Ribier reference where NADG, *per se*, is added directly to the vehicle.

The Examiner finds that the addition of a mixture of NADG and cholesterol sulfate to a vehicle is considered to be well within the skill of the ordinary artisan. However, the addition of many mixtures to a vehicle have been found patentable because as it pertains to obviousness, an inventive concept is patentable if it is not taught or suggested by a cited prior art reference or known generally. Thus, while Applicants refrain from comment regarding the general task of adding a mixture to a vehicle, what is at issue with respect to the present inventive concept is whether one of ordinary skill in the art would was in possession of the addition of a mixture of NADG and cholesterol sulfate to a vehicle. Applicants assert that the cited prior art demonstrates that the addition of the specific combination of NADG and cholesterol sulfate to a vehicle was not in the possession of one of ordinary skill in the art as it merely suggests that the cholesterol sulfate is useful in the lipid bilayer of a vesicle holding NADG inside of it. None of the cited prior art references teach or suggest adding a combination of NADG and cholesterol sulfate as a mixture directly to a vehicle. In particular, the '166 Ribier reference fails to teach an amino sugar added directly to the vehicle, and therefore, there is no teaching or suggestion of the mixture of cholesterol sulfate and an amino sugar added to the vehicle by the '166 reference.

U.S. Patent Nos. 5,650,166, 6,159,381, and 5,702,691 ("the three references")

The Examiner finds that Claims 10 – 12 and 20 are not patentable over the combination of the three references (individually referred to as the '166, the '381, and the '691 references") for reasons of record stated in the Office Action of November 5, 2002. Further, the Examiner claims that the motivation to make the combination of the three references is provided sufficiently in the Office Action of November 5, 2002. However, in Applicants' previous response it was pointed out that neither of the additional references remedied the defect of the '166 Ribier reference in that it failed to teach or suggest the addition of the NADG directly to a vehicle because the '166 Ribier reference merely taught how to incorporate NADG inside of a lipid vesicle, and then subsequently the incorporation of the vesicle containing NADG inside into a vehicle. However, Applicants comment herein on the motivation presented in the Office Action of November 5, 2002. As noted by the Examiner in the Office Action of November 5, 2002, the motivation stems from the benefit of anti-inflammatory properties as those taught in the '691 reference and the anti-acne properties as taught in the '381 reference in a cosmetic formulation. The missing ingredients have art recognized suitability in cosmetic formulations. Therefore, the selection of known materials based on their suitability for their intended uses is determined to be *prima facie* obvious. However, the uses of the materials in the '166 Ribier reference is different than the use in the present invention, and therefore, the '166 Ribier reference fails to teach or suggest the present invention, and the '381 and the '691 references fail to remedy this defect.

As discussed above the cholesterol sulfate of the '166 Ribier reference is taught as part of the membrane of the lipid vesicle that holds the deep down active agent, NADG, contained within the vesicle. This is different than a simple mixture of NADG with cholesterol sulfate like that of the present invention. Thus, the uses of NADG in the '166 Ribier reference as an active encapsulated in a lipid vesicle is different than the mixture of NADG with cholesterol sulfate for two reasons. First, the '166 Ribier reference fails to place in possession of one of ordinary skill in the art the direct mixture of NADG and cholesterol sulfate. While the cholesterol sulfate is part of the membrane of the lipid vesicle it is not mixed with NADG as it remains a separate entity inside of the membrane layers of the lipid vesicle. Second, while the NADG is encapsulated inside of the membrane layers it is not directly added to a vehicle because the NADG remains protected from the vehicle by virtue of its presence inside of the membrane layers.

As found by the US Supreme Court in *United States v. Adams et al.*, 148 USPQ 479, 482-84 (US SupCt 1966), the case of *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) is inapposite in a situation where the subject matter of the prior art is a completely different design type. In *Adams*, magnesium in place of zinc and copper as a substitute for silver were found not to be mere equivalent substitutions in batteries the design of which between that of the prior art and the invention at issue were of a completely different type. *Adams*, at 483. As in *Adams*, the design and use of cholesterol sulfate in a membrane layer of a lipid vesicle encapsulating NADG is completely different than the type of design and use of the present invention whereby cholesterol sulfate is simply combined with NADG and as a mixture are added directly to a vehicle. Thus, because the mixture of cholesterol sulfate and NADG is not taught or suggested by the '166 Ribier reference, the '166 Ribier reference fails to render the present invention obvious. Further, the '381 and the '691 references fail to teach or suggest the direct addition of a mixture of NADG and cholesterol sulfate to a vehicle because the Examiner in the Office Action of November 5, 2002 notes that the '381 reference teaches the use of sclareolide in topical formulations particularly for acne, and the '691 reference teaches that white birch extract is a known anti-inflammatory agent. The teachings of the '381 and the '691 references fail to remedy the defect of the '166 Ribier reference, and therefore, the combination of the cited references fail to establish a *prima facie* case of obviousness.

U.S. Patent Nos. 5,925,364 and 5,411,742 ("the two references")

The third obviousness rejection is based on the two references (individually referred to as the '364 Ribier and the '742 references").

The Examiner rejects Claims 1, 3 - 4, 6 – 9, 11 and 18 under 35 U.S.C. 103(a) as being unpatentable over the '364 Ribier reference in view of the '742 reference. Applicants assert that the argument applied to the '364 Ribier reference previously in their Response of February 5, 2003 applies herein because of the reference to the disclosure of oily globules coated with a lamellar liquid crystal coating and the similarity with the lipid vesicles of the '166 Ribier reference. Specifically, the '364 Ribier reference discloses an emulsion composition that has oily globules with a lamellar liquid crystal coating dispersed in an aqueous phase. Like that of the '166 Ribier reference, the composition as described in the claims can include materials such as alkali metal salts of cholesteryl sulphate as the ionic amphiphilic lipid as one of the layers coating an active (i.e., similar to the membrane layers of the '166 Ribier vesicles). Therefore, the oily globules of the '364 Ribier reference, like that of the '166 Ribier reference, fails to teach or suggest the mixture of NADG and cholesterol sulfate in the present invention.

The '364 Ribier compositions can contain as a fatty substance a keratolytic agent. One of the many keratolytic agents listed is retinol and salicylic acid which the Examiner notes are known exfoliants. Therefore, according to the Examiner, the '364 Ribier reference in combination with the '742 reference is obvious to one of ordinary skill in the art. Motivation is, according to the Examiner, based in using the fatty acid and cholesterol of the '364 Ribier reference since fatty acids are known to be used in cosmetic compositions for treating skin. Further, the Examiner notes that cholesterol is a well know ingredient in a cosmetic. Therefore, one of ordinary skill in the art would have reasonably expected that a combination of the '364 Ribier compositions with the '742 compositions would be useful for the same purpose, treating skin, and would improve the therapeutic effect of treating the skin. Applicants assert that the basis of motivation to combine the references is misplaced because the combination of the '364 Ribier and the '742 references does not render the present invention.

Both the '364 Ribier reference and the '742 reference disclose lipid vesicle/lamellar systems. Thus, neither reference alone or in combination teaches or suggests the mixture of NADG and cholesterol sulfate like that of the present invention for the reasons presented above with respect to the '166 Ribier reference. Basically, the lipid vesicles/lamellar systems separate the NADG (exfoliant) from the cholesterol sulfate because the cholesterol sulfate is part of the membrane layer of the vesicle or lamellar system. As it is noted by the Examiner in the present action both the '364 Ribier reference and the '742 reference disclose metal salts of cholesterol sulphate. There is a basic reason why both references make such a disclosure – namely both references disclose lipid vesicle/lamellar systems whereby the layers of the vesicle or lamellar system contains cholesterol sulfate. The capsule formed by the membrane holds within it an active which can include an exfoliant. However, one of ordinary skill in the art would not find a disclosure of encapsulating an exfoliant within a lipid vesicle to be a teaching of a mixture of the exfoliant with cholesterol sulfate found in the membrane layer of the vesicle. Thus, Applicants assert that the scope of the '364 Ribier and the '742 references is to be interpreted in view of how one of ordinary skill in the art would make such an interpretation. Evidence of this interpretation is found in the cited references wherein it is disclosed that the cholesterol sulfate is part of the membrane forming the vesicle and the exfoliant is an active encapsulated therein.

> See column 4, lines 42 – 50, of the '364 Ribier reference "[w]hen the compositions according to the invention are used for cosmetic treatment . . . the active agent contained in the oily phase is . . . keratolytic agents. The oily phase of the '364 Ribier reference is coated with a lamellar liquid crystal coating that can contain cholesterol sulfate derivatives. See column 3, line 36 to column 4, line 15, of the '364 Ribier reference "[t]he coating . . . of the oily globules preferably requires the

> use of a total amount of hydrophilic surface-active agent, of lipophilic surface-active agent and of ionic amphiphilic lipid . . . " and "[t]he ionic amphiphilic lipid used within the context of the present invention is . . . metal salts of cholesteryl sulphate. . ."
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> In the same fashion, see column 3, line 64 to column 6, line 20, of the '742 reference "the constituent lipid phase of the membranes of the vesicles of the dispersion comprises, in a known manner, at least one amphiphilic lipid . . . cholesterol sulphate. . . " And, see column 3, lines 1 to 8, "[t]he subject of the invention is therefore a composition for the treatment of acne by topical application containing . . . vesicles of amphiphilic lipid(s) consisting of a lipid phase membrane encapsulating an aqueous phase E, the lipid phase containing as additive a charged lipid . . . [containing] at least one salicylic acid derivative of formula: . . . "

Clearly, it can be seen from the inventions described by both the '364 Ribier reference and the '742 reference that these are both inventions related to lipid vesicles/ lamellar systems like that of the '166 Ribier reference. Therefore, the combination of these references for reasons stated above, fail to teach or suggest a mixture of NADG and cholesterol sulfate as in the present invention.

Finally, even if the interpretation of one of ordinary skill in the art were that a lipid vesicle containing cholesterol sulfate in the membrane layer and NADG encapsulated therein was equivalent to the mixture of the present invention, Applicants assert that it would be rebutted by the surprising results of the present invention. The Examiner notes in the present action that the Example in the present specification does not provide clear and convincing evidence of nonobviousness or unexpected results over the cited prior art because there is no direct comparison of the same. However, as Applicants have pointed out in the present response, the two systems are not the same and there was no reason to believe that the mixture of the ingredients of the present invention directly in a vehicle would necessitate a comparison with a lipid vesicle as these are two completely different systems. The present invention focuses on the finding that two ingredients, the cholesterol sulfate and the amino sugar, although they have opposing activities, when added as a mixture to a pharmaceutical or cosmetic vehicle, do not neutralize one another's activities, but rather their activity occurs in tandem, and can improve or maintain a healthy skin barrier. This benefit cannot even be addressed with the cited references because these two materials are not in fact mixed. Rather, they are separated such that one, the cholesterol sulfate, is part of a protective membrane that encases the other, the NADG. The whole point of the lipid vesicles/lamellar systems of the cited references is to protect and prevent the active inside from interacting with anything else. Thus, a comparison of this kind would be futile.

CONCLUSION

Because none of the cited references alone nor in combination would lead one of ordinary skill in the art to the compositions and methods of the present invention, a *prima facie* case of obviousness has not been established. Applicants request therefore, that the Examiner's rejection under §103 be withdrawn. In view of the arguments presented above in the present submission, the claims are believed to be in condition for allowance, and issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,

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